Classifier construction via. Boosting

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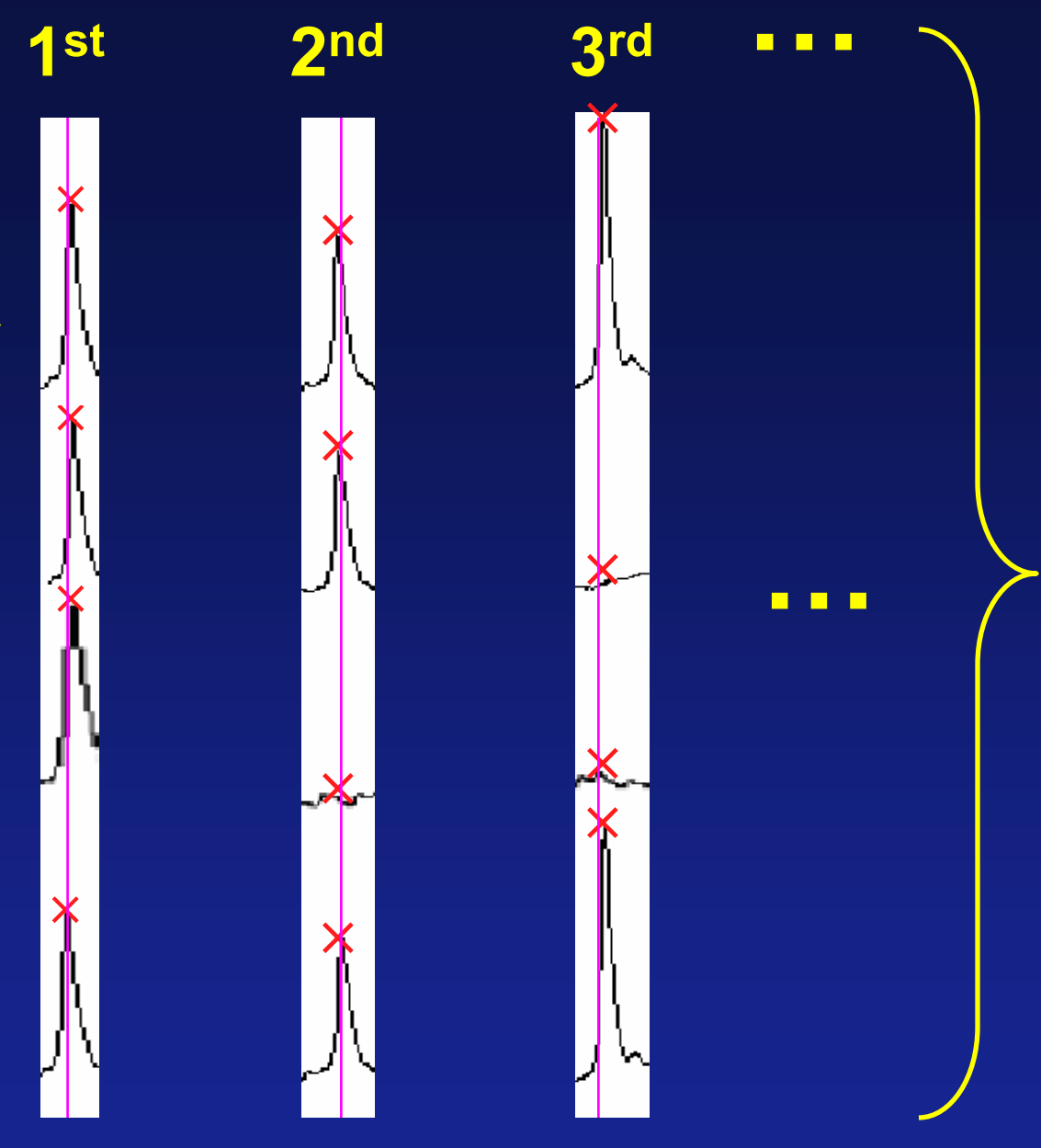
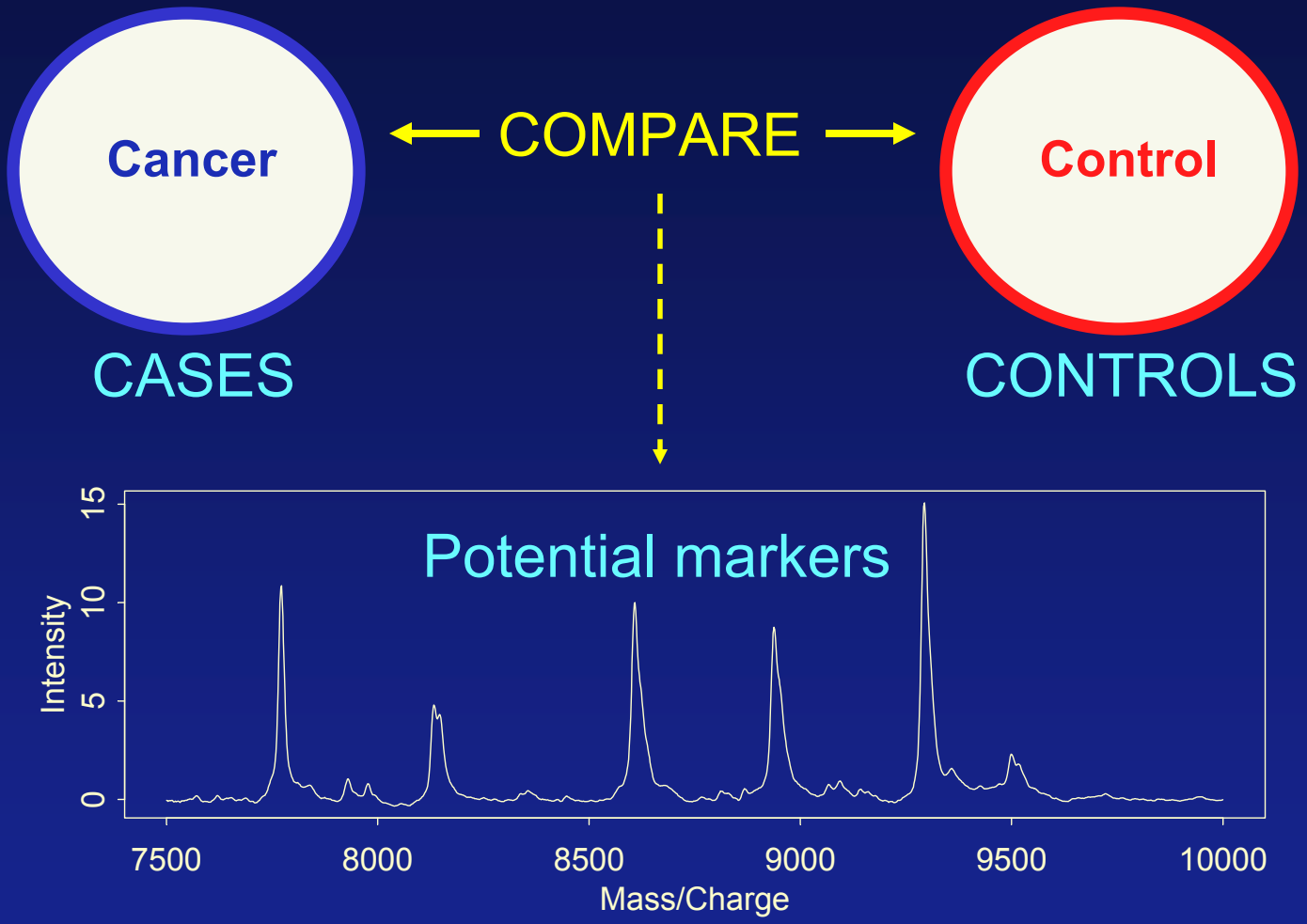


The aligned datase
for
searching
signature markers
profiles

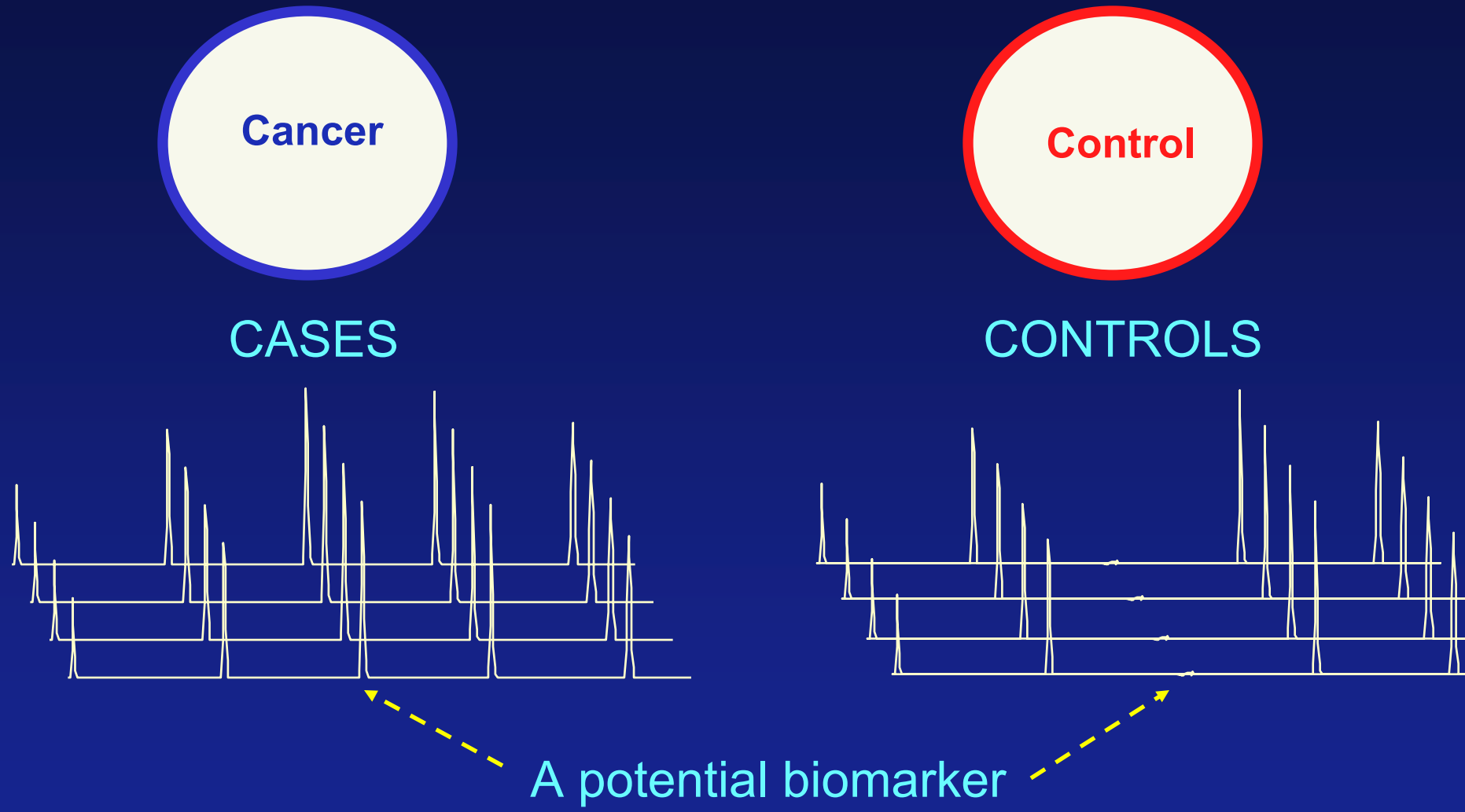
Completion of pre-
analysis processing

Yasui et al. J. Biomed. & Biotech
(Special Issue on Proteomics) 20

Basic Study Design



Biomarker Discovery



Phases of Biomarker Discovery & Validation

Pepe et al. JNCI 2001

Pre-clinical Exploratory	***PHASE 1***	*Promising directions identified*
Clinical Assay Validation	***PHASE 2***	*Clinical assay detects established disease*
Retrospective Longitudinal	***PHASE 3***	*Biomarker detects pre-clinical disease and a "screen positive" rule defined*
Prospective Screening	***PHASE 4***	*Extent and characteristics of disease detected by the test and the false referral rate are identified*
Cancer Control	***PHASE 5***	*Impact of screening on reducing burden of disease on population is quantified*

100% sensitivity & specificity

in classifying cases vs. controls

$\neq$

Identification of biomarkers for cases

Three Principles of Case-Control Design
(Wacholder et al. Am J Epidemiol 1992)

1. A common study base for cases and controls
2. Controlling for confounding effects
3. Comparable accuracy and precision in exposure measurements

1. Common Study Base

- ○ Define a common study base (who, where, when) and sample both cases and controls from it

- × Cases and controls from different institutions
- × Cases from a past study, controls from an ongoing study

⇨ Disease is not the only difference between cases and controls

2. Controlling for confounding

- ○ Balance age and race between cases and controls (or adjust for in the analysis)

- × Study base = 30-75 women in Montreal in 2003
  Breast cancer cases = Tend to be older
  Controls = Younger

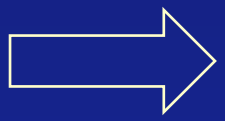
⇨ Markers for age, not cancer, will distinguish cases and controls

3. Comparable measurement errors

- Unify the sample collection, processing, storage, and assay methods for cases and controls.

  Balance the use of machines, technicians, chips, and wells between cases and controls.

If not,

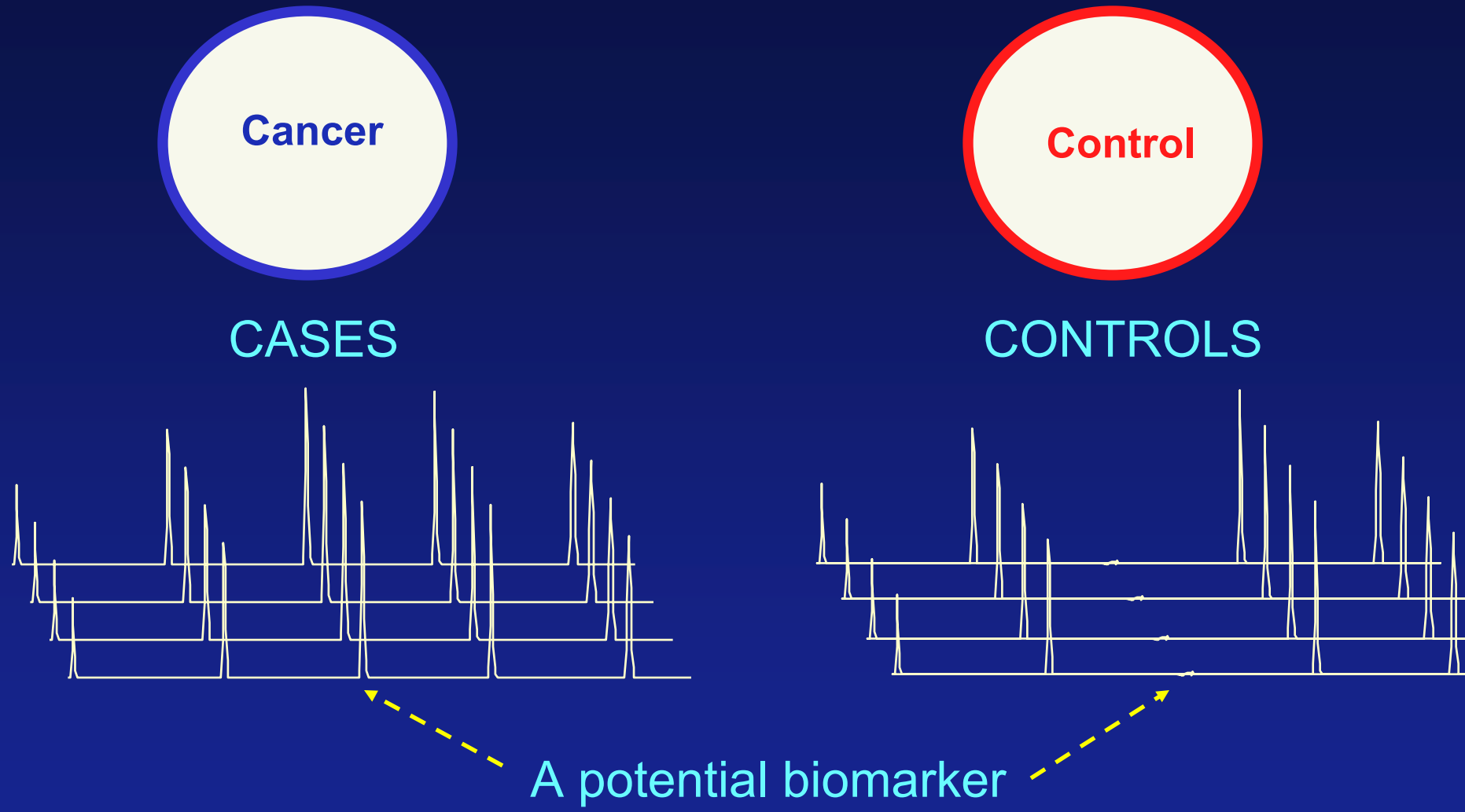


True marker-disease relation is distorted

Use of multiple markers

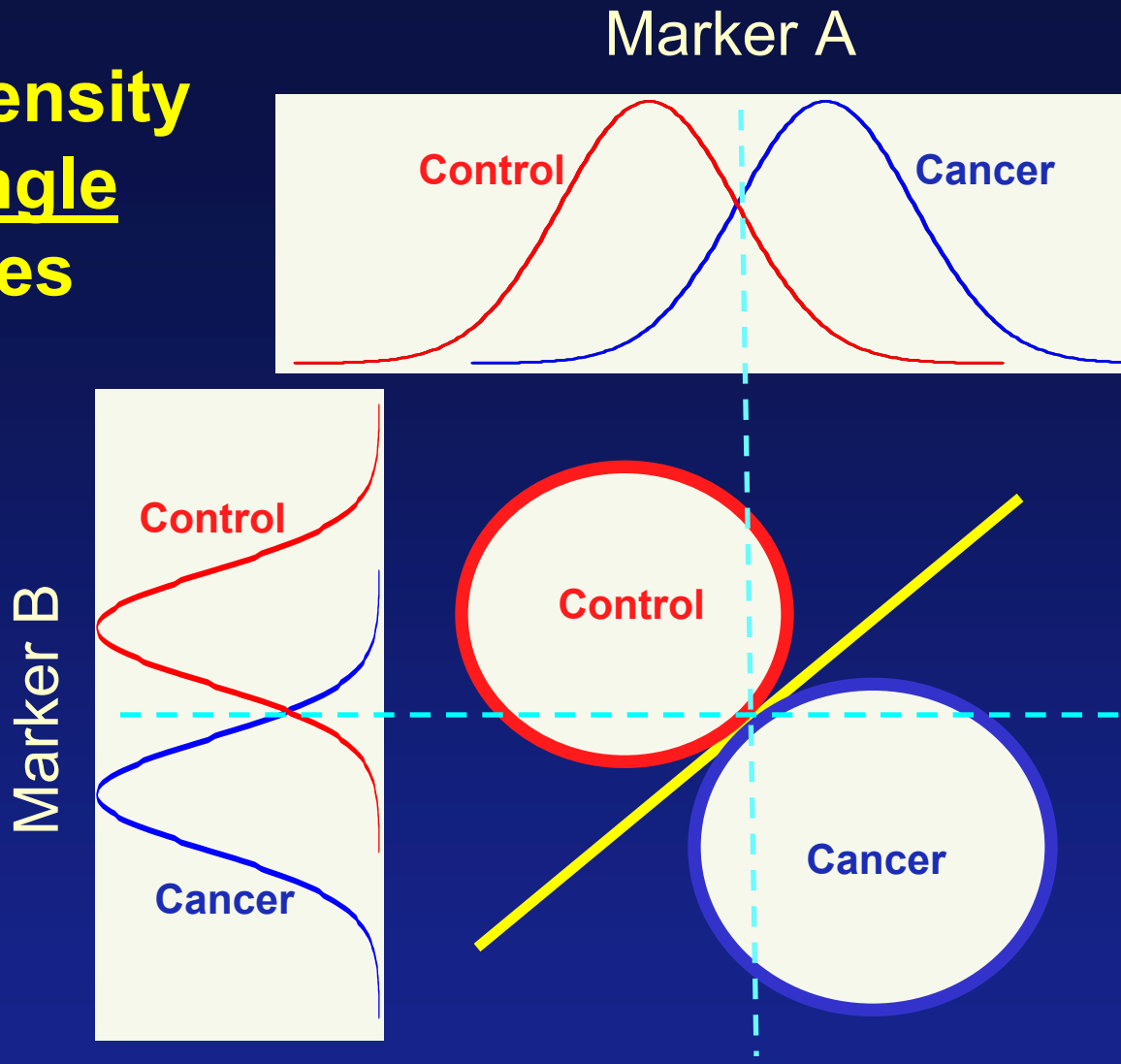
in classifying disease classes

Biomarker Discovery



Likely overlap of intensity distributions of a single marker between cases and controls

Need to combine information from multiple markers!

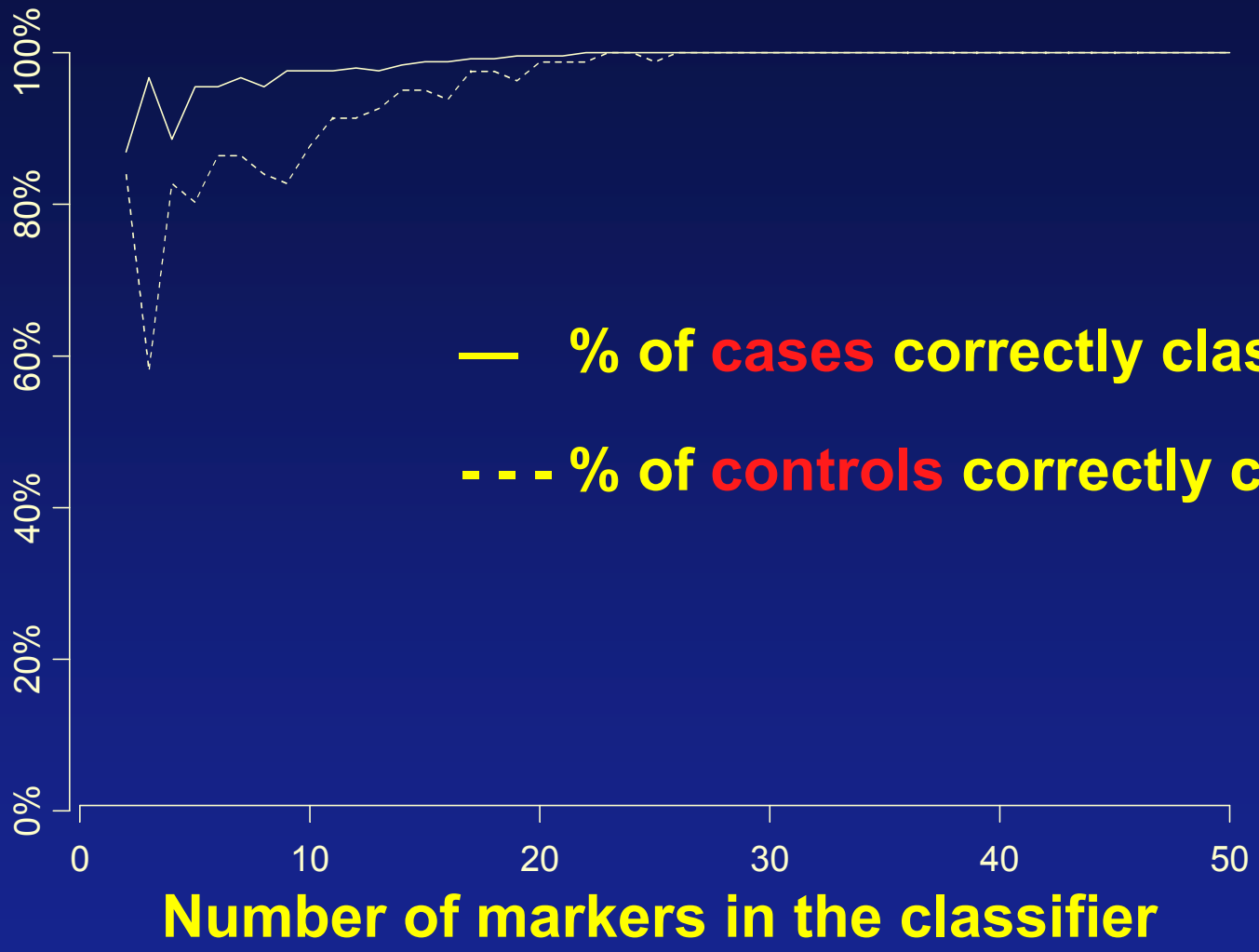


Building Classifiers

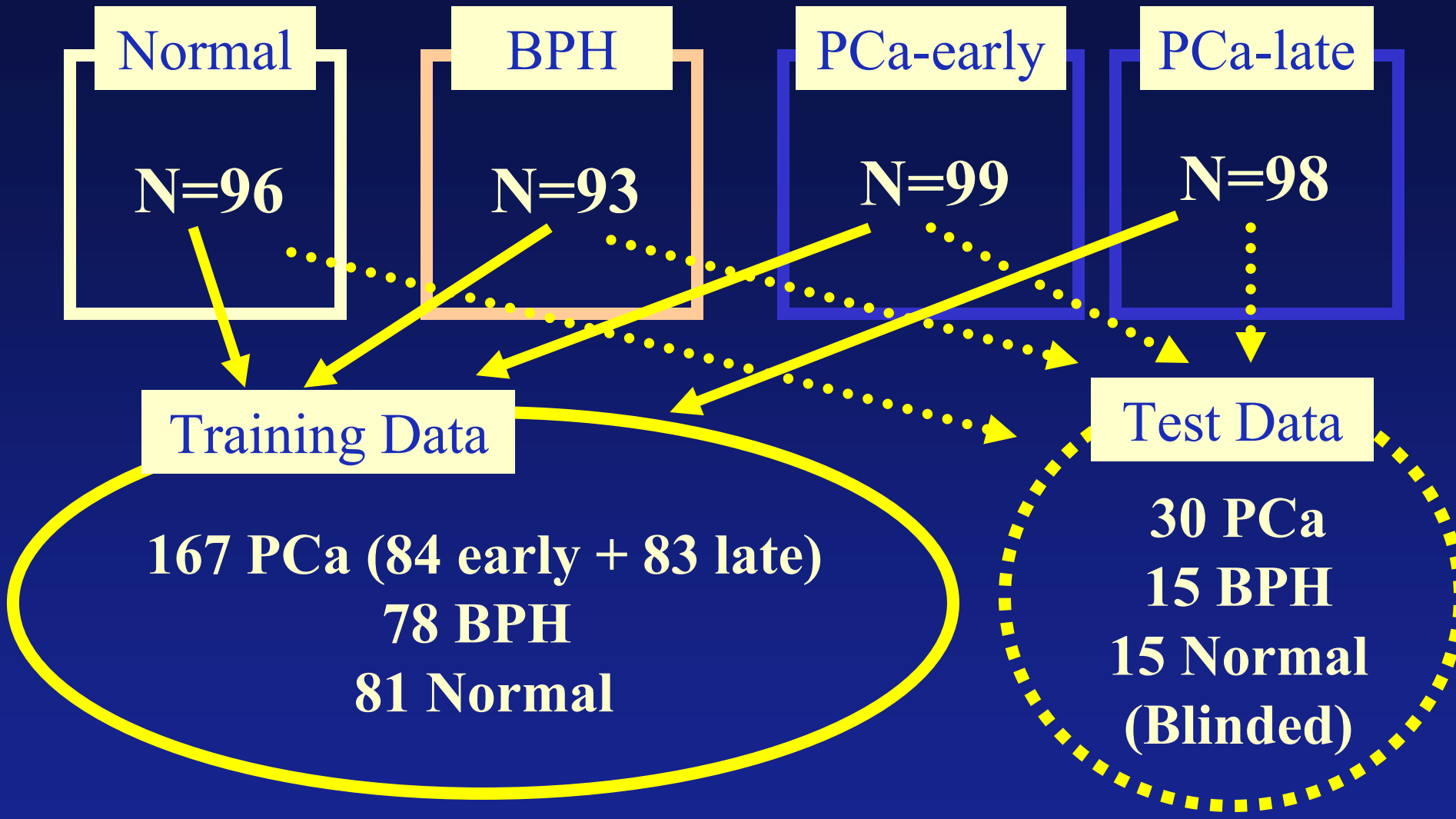
- Classical Discriminant Analysis
- Logistic Regression
- CART
- Neural Network
- Support Vector Machine
- Boosting

…

ancer vs. control classification in a given datas



The design of the EVMS biomarker analysis

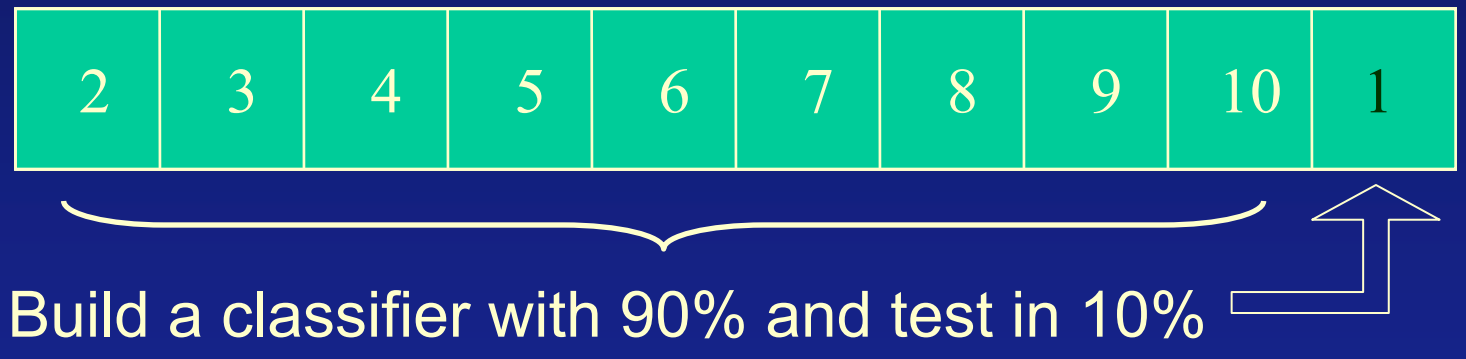


How to assess over-fitting in the training set ?

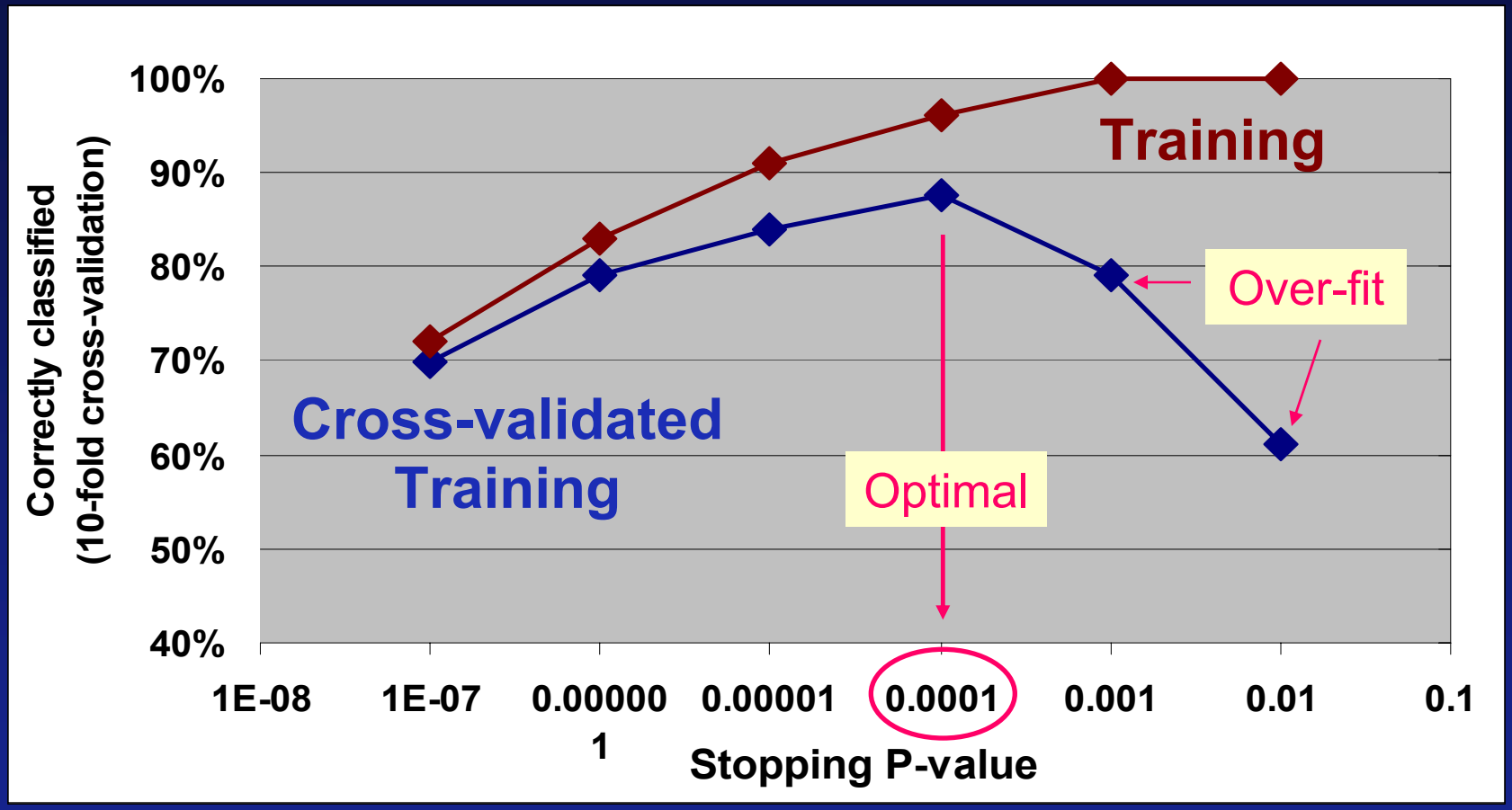
- Cross-validation of the training data

  Use 90% to form the marker set & 10% to test

  Repeat 10 times and summarize



Logistic regression with forward variable selection with various stopping p-values



Use of the test set

Enable unbiased assessment of classification erro

if no modification/selection of the classifier-construction method is made with the test set

e.g., Construct 2 classifiers with the training set and report the one with the better test-set performance

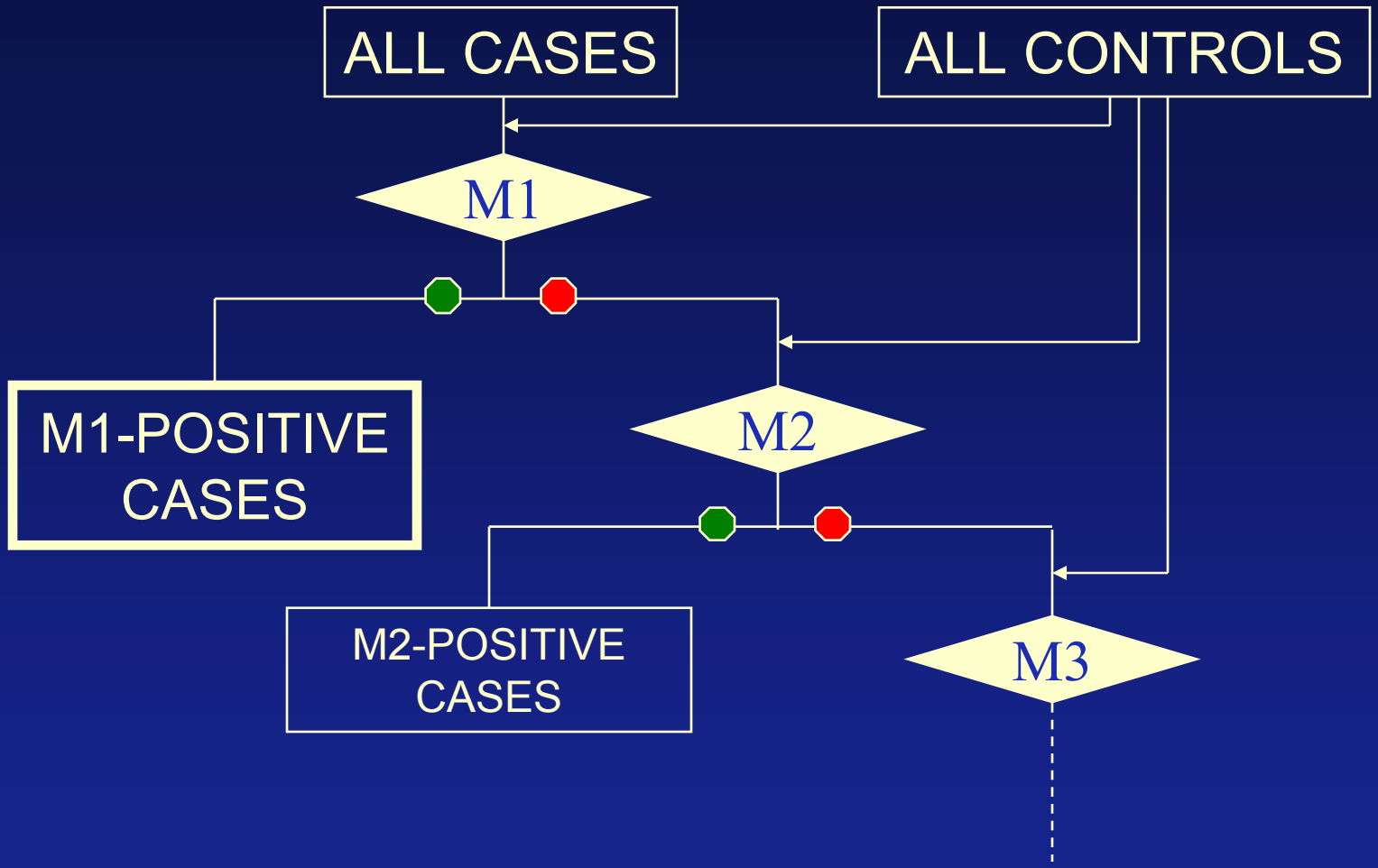
(2 feature selection methods, stepwise stopping, etc

Boosting for supervised and partially supervised learning

Method for classifier building and

its modification for partially-incorrect class labels

Heterogeneity / subtypes within cancer



Real AdaBoost Algorithm ($y^* = 1$ vs. $y^* = -1$)

Friedman, Hastie, Tibshirani (Annals of Statistics, 2000)

1. Let $w_i \equiv 1/N$ for $i = 1, 2, \ldots, N$
2. Repeat for $m = 1, 2, \ldots, M$
   - Fit a classifier with weights $\{w_i\}$ to get
     $p_m(x) = \Pr(Y^*=1|x, \{w_i\})$
   - Set $w_i = w_i \times \exp\{-0.5\, y_i^* \times \text{logit}\, p_m(x_i)\}$
   - Renormalize $\{w_i\}$ such that $\sum_i w_i = 1$
3. The final classifier:
   $\eta_M(x) = \text{logit}\, p_1(x) + \text{logit}\, p_2(x) + \ldots + \text{logit}\, p_M(x) > c$

Real AdaBoost with Logistic Regression

$$(\alpha_m, \beta_m, X^{(m)}) = \arg\min_{(\alpha,\beta,X)} \sum_i \underbrace{e^{-\frac{y_i^*}{2}\sum_{j=1}^{m-1}(\hat{\alpha}_j + \hat{\beta}_j X_i^{(j)})}}_{\text{Weights}} \underbrace{\ln\{1 + e^{-y_i^*(\alpha+\beta X_i)}\}}_{\text{Negative log-likelihood}}$$

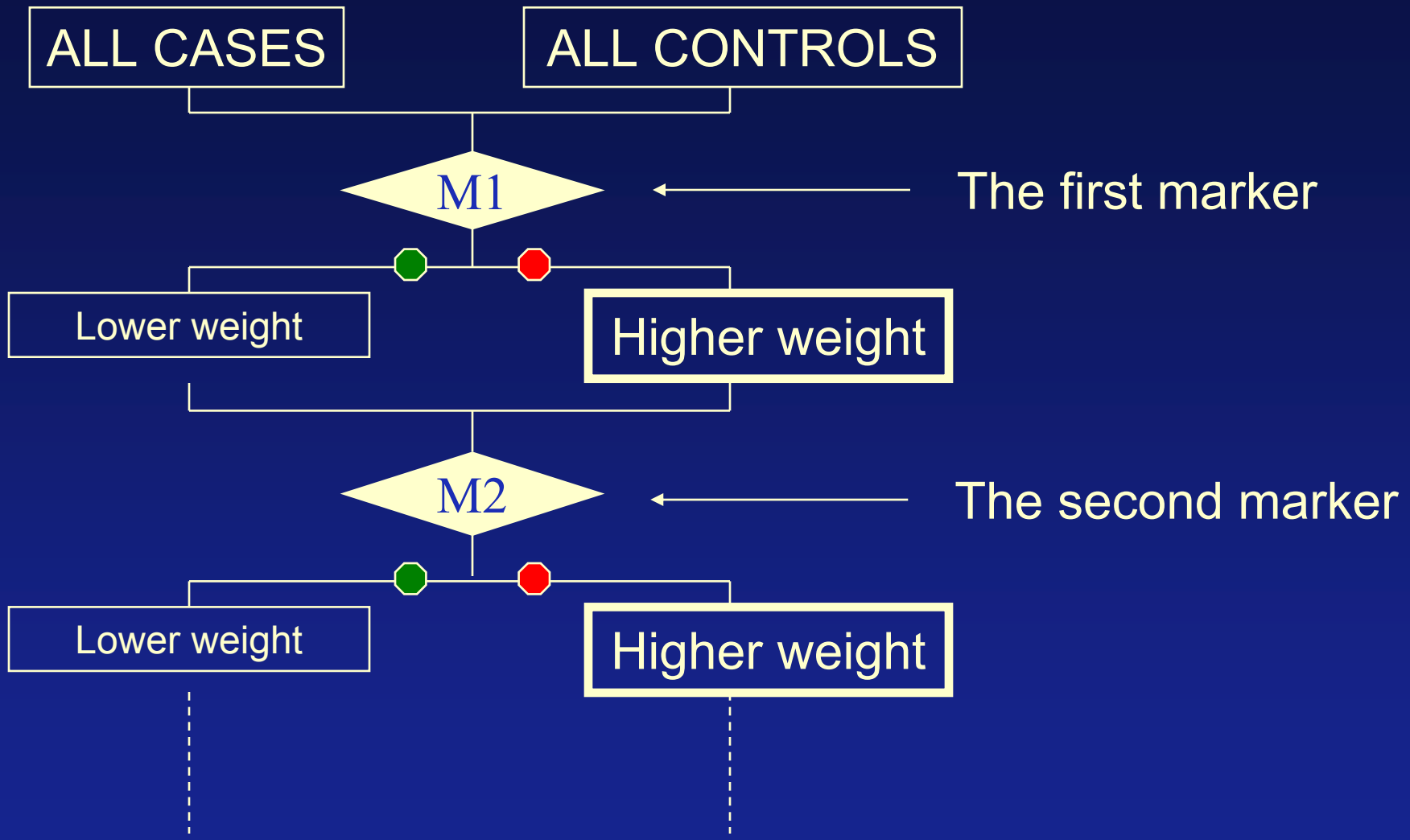
$w_i = w_i \times \exp\{-0.5\, y_i \times \text{logit}\, p_{m-1}(x_i)\}$

$= w_i \times \exp\{-0.5\, y_i \times (\alpha_{m-1} + \beta_{m-1}\, x_i)\}$

$= \exp\{-0.5\, y_i \sum_{j=1,\ldots,(m-1)} (\alpha_j + \beta_j\, x_i)\}$

Yasui et al. (Biostatistics, 200

Boosting algorithm



Performance of the boosting classifier

(1st stage: Abnormal vs. Normal)

Correct classification

	Training dataset	Test dataset
Cancer/BPH	245/245 (100%)	44/45 (97.8%)
Normal	81/ 81 (100%)	15/15 (100%)

Why does this work?

AdaBoost = “Best off-the-shelf classifier”

(Brieman)

$$(\alpha_m, \beta_m, X^{(m)}) = \arg\min \sum \mathrm{e}^{-\frac{y_i^*}{2}\sum_{j=1}^{m-1}(\hat{\alpha}_j + \hat{\beta}_j X_i^{(j)})} \ln\{1 + \mathrm{e}^{-y_i^*(\alpha+\beta X}$$

oosting = Stage-wise minimization of a loss function

$$= \arg\min_{(\alpha,\beta,X)} \sum_i L_i^*(y_i^*, \eta_{\phi_m}(X_i^{(m)}))$$

$$(\alpha_m, \beta_m, X^{(m)}) = \underset{(\alpha,\beta,X)}{\arg\min} \sum_i L_i^*(y_i^*, \eta_{\phi_m}(X_i^{(m)}))$$

$$= \underset{(\theta=(\alpha,\beta),X)}{\arg\min} \sum_i L_i^*(y_i^*, \eta_{(\theta,\phi_{m-1})}(X, X_i^{(m-1)}))$$

$$\phi_{(m-1)} = (\theta_1, \ldots, \theta_{(m-1)})$$

Previous stages' parameters

$$X^{(m-1)} = (X^1, \ldots, X^{(m-1)}$$

Previous stages' biomarkers

FIXED

$$(\alpha_m, \beta_m, X^{(m)}) = \underset{(\theta=(\alpha,\beta),X)}{\arg\min} \sum_i L_i^*(y_i^*, \eta_{(\theta,\phi_{m-1})}(X, X_i^{(m-1)}))$$

fixed fixed

Boosting = Stage-wise minimization of a loss function L^* given previously selected biomarkers $X^{(m-1)}$ and their parameters $\phi_{(m-1)}$

Classifier changes slightly at each stage = Slow learning

$$(\alpha_m, \beta_m, X^{(m)}) = \arg\min_{(\alpha,\beta,X)} \sum_i \mathrm{e}^{-\frac{y_i^*}{2}\left[\left\{\sum_{j=1}^{m-1}(\hat{\alpha}_j + \hat{\beta}_j X_i^{(j)})\right\} + (\alpha + \beta X_i)\right]}$$

$$= \arg\min_{(\alpha,\beta,X)} \sum_i \mathrm{e}^{-\frac{y_i^* \, \eta_{\phi_m}(X_i^{(m)})}{2}}$$

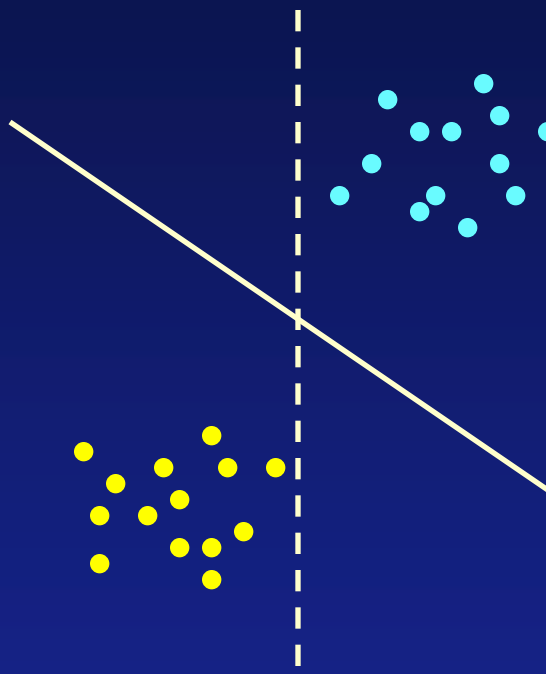
$$= \arg\min_{(\alpha,\beta,X)} \sum_i L_i^*(y_i^*, \eta_{\phi_m}(X_i^{(m)}))$$

Does this form of the loss function make sense?

Large margin classifiers

Margin$_i \equiv y_i \ \eta(x_i)$

- $>$ 0 if $\eta(x_i)$ is correct
- $<$ 0 if $\eta(x_i)$ is wrong



- Higher confidence in classification
- Increased generalizability

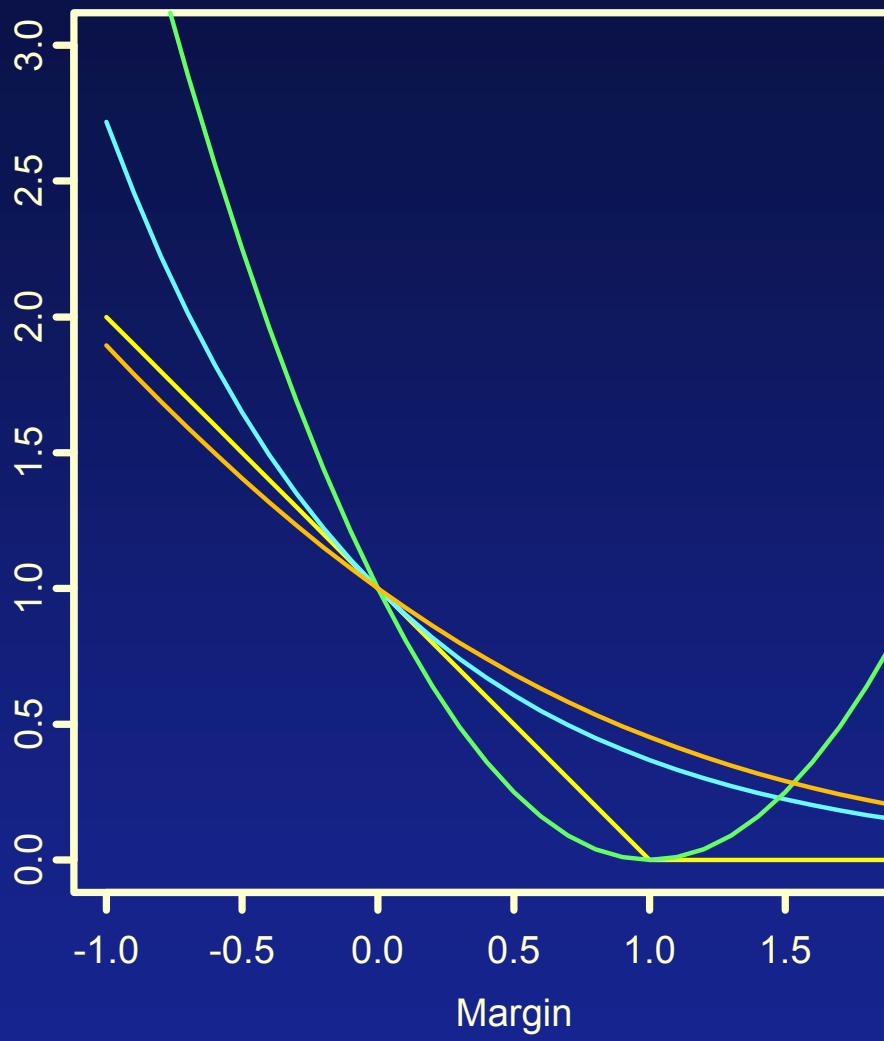
Large margin classifiers

SVM = min $\sum_i$ max(0,1-margin$_i$)

AdaBoost = min $\sum_i$ e$^{-\text{margin}i}$

Logistic = min $\sum_i$ log(1+e$^{-\text{margin}i}$)

NN = min $\sum_i$ (1-margin$_i$)^2



Discrete AdaBoost Algorithm ($y^* = 1$ vs. $y^* = -1$)

1. Let $w_i \equiv 1/N$ for $i = 1, 2, \ldots, N$
2. Repeat for $m = 1, 2, \ldots, M$
   - Fit a base classifier $f_m(x_i) \in \{-1,1\}$ (e.g., a decision tree) with weights $\{w_i\}$
   - $ERR_m = \sum w_i \, 1\{y_i \neq f_m(x_i)\}$
   - $C_m = \log\{(1-ERR_m)/ERR_m\}$
   - Set $w_i = w_i \times \exp\{-0.5 \, C_m \, y_i^* \times f_m(x_i)\}$
   - Renormalize $\{w_i\}$ such that $\sum_i w_i = 1$
3. The final classifier: $C_1 f_1(x) + C_2 f_2(x) + \ldots + C_M f_M(x) > c$

It worked well for Cancer/BPH vs. Normal

But …

Performance of the boosting classifier

(2nd stage: Cancer vs. BPH)

Correct classification

	Training dataset	Test dataset
Cancer	160/167 (95.8%)	28/30 (93.3%)
BPH	70/ 78 (89.7%)	7/15 (46.7%)

European Prostate Cancer Detection Study

Protocol: Biopsy 1,051 men with PSA 4-10 ng/ml

If negative, take another biopsy 6 weeks later

If negative again, take another 8 weeks later

Cancer detection: 231 were detected by Biopsy 1

83 were detected by Biopsy 2

36 were detected by Biopsy 3

119 cance
missed b
Biopsy 1

∴ A single biopsy can miss > 1/3 of cancers in PSA 4-10 patients

Cancer label = 100% correct

Non-cancer label < 100% correct

≡ Partially Supervised Learning

How can we “learn” from potentially partially mislabeled data?

- If correct labels y_i^*s are available:

$$(\alpha_m, \beta_m, X^{(m)}) = \arg\min_{(\alpha,\beta,X)} \sum_i \underbrace{e^{-\frac{y_i^*}{2}\sum_{j=1}^{m-1}(\hat{\alpha}_j + \hat{\beta}_j X_i^{(j)})}}_{\text{weights}} \underbrace{\ln\{1 + e^{-y_i^*(\alpha+\beta X_i)}\}}_{\text{- log-likelihood}}$$

High (low) weights for incorrectly (correctly) classified observations

Results of $(m-1)^{th}$ classification $\Rightarrow$ Who should "speak louder" at m^{th} stage

- If correct labels y_i^*s are NOT available:

$\Rightarrow$ We cannot determine whether the $(m-1)^{th}$ classification was correct or not

$\Rightarrow$ Unclear who should speak louder at the m^{th} stage

PROPOSAL

Let the observations that are likely to be misclassified at $(m-1)^{th}$ stage speak louder at m^{th} stage

$$\Pr[y_i^* = -1 \mid \phi_{(m-1)}, X^{(m-1)}, y] \times e^{-\frac{y_i^*}{2}\sum_{j=1}^{m-1}(\hat{\alpha}_j + \hat{\beta}_j X_i^{(j)})} \ln\{1 + e^{-y_i^*(\alpha+\beta X_i}$$

-1 (×2)

Loss if $y_i^* = -1$

+

$$\Pr[y_i^* = 1 \mid \phi_{(m-1)}, X^{(m-1)}, y] \times e^{-\frac{y_i^*}{2}\sum_{j=1}^{m-1}(\hat{\alpha}_j + \hat{\beta}_j X_i^{(j)})} \ln\{1 + e^{-y_i^*(\alpha+\beta X_i}$$

1 (×2)

Loss if $y_i^* = 1$

- If correct labels y_i^*s are available:

$$\arg\min_{(\underset{\%}{\theta}=(\alpha,\beta),X)} \sum_i L_i(\underset{\%}{\theta}, X; \underset{\%}{\phi}_{(m-1)}, \underset{\%}{X}^{(m-1)}, y_i^*)$$

- If correct labels y_i^*s are NOT available:

$$\arg\min_{(\underset{\%}{\theta}=(\alpha,\beta),X)} \sum_i \sum_{y_i^*=-1}^{y_i^*=1} L_i(\underset{\%}{\theta}, X; \underset{\%}{\phi}_{(m-1)}, \underset{\%}{X}^{(m-1)}, y_i^*) \Pr[y_i^* \mid \underset{\%}{\phi}_{(m-1)}, \underset{\%}{X}^{(m-1)},$$

$$\arg\min_{(\underset{\%}{\theta}=(\alpha,\beta),X)} \sum_i E[L_i(\underset{\%}{\theta}, X; \underset{\%}{\phi}_{(m-1)}, \underset{\%}{X}^{(m-1)}, y_i^*) \mid \underset{\%}{\phi}_{(m-1)}, \underset{\%}{X}^{(m-1)}, \underset{\%}{y}] \Rightarrow \mathrm{E}$$

Yasui et al. (Biometrics, 2004

Design of the simulation study

Normal

N=81

$\{y_i^*\}$

Cancer / BPH

N=245

Study (1): N=49 (>50% of Normal)
Study (2): N=98 (>100% of Normal)

"Normal"

(1) N=130

(2) N=179

$\{y_i\}$

Cancer / BPH

(1) N=196

(2) N=147

Test Data

45 Ca/BPH

15 Normal

Questions in the simulation study

Q1: Can we recover the cancer/BPH samples that were incorrectly labeled as “normal”?

Q2: How do the classifiers constructed from the incorrectly labeled training dataset perform when tested against the test dataset?

Learning methods compared

(1) Forward-selection logistic regression with BIC as the model-selection criteria

(2) Real AdaBoost with logistic regression (stopped at m=100th iterations)

(3) EM-Boost with P_0 = 0.1, 0.3, 0.5 (stopped at m=100th iterations)

Study (1): Training Dataset Results

LEARNING METHOD	AREA UNDER THE ROC CURVE (P-VALUE)	SENSITIVITY AT 95% SPECIFICITY
Forward-selection BIC	0.9584 (0.0393)	65.4
Real AdaBoost	0.9741 (Reference)	79.0
EM-Boost		
$P_0 = 0.1$	0.9926 (0.0024)	97.5
$P_0 = 0.3$	0.9932 (0.0040)	97.5
$P_0 = 0.5$	0.9919 (0.0068)	96.3

Study (1): Test Dataset Results

LEARNING METHOD	AREA UNDER THE ROC CURVE (N = 60)	PREDICTION ERROR (N = 60)
Forward-selection BIC	0.807	19 (31.7%)
Real AdaBoost	0.816	15 (25.0%)
EM-Boost		
$P_0 = 0.1$	0.925	6 (10.0%)
$P_0 = 0.3$	0.919	7 (11.7%)
$P_0 = 0.5$	0.936	5 (8.3%)

Study (2): Training Dataset Results

LEARNING METHOD	AREA UNDER THE ROC CURVE (P-VALUE)	SENSITIVITY AT 95% SPECIFICITY
Forward-selection BIC	0.9064 (0.0018)	50.6
Real AdaBoost	0.9462 (Reference)	58.0
EM-Boost		
$P_0 = 0.1$	0.9623 (0.0358)	75.3
$P_0 = 0.3$	0.9740 (0.0015)	80.2
$P_0 = 0.5$	0.9812 (0.0001)	82.7

Study (2): Test Dataset Results

LEARNING METHOD	AREA UNDER THE ROC CURVE (N = 60)	PREDICTION ERROR (N = 60)
Forward-selection BIC	0.671	28 (46.7%)
Real AdaBoost	0.790	26 (43.3%)
EM-Boost		
$P_0 = 0.1$	0.880	12 (20.0%)
$P_0 = 0.3$	0.913	8 (13.3%)
$P_0 = 0.5$	0.920	11 (18.3%)

Summary

- Pre-analysis processing is crucial for a proper analysis
- Avoiding overfitting is the key in classifier building with multiple biomarkers
- In biomedical applications, imperfect class labels are common
- EM-Boost modifies the boosting algorithm to accommodate potential mislabeling: allows “learning” in partially supervised settings

$$\Pr[y_i^* \mid \underline{\phi}_{(m-1)}, \underline{X}^{(m-1)}, \underline{y}]$$

$$\begin{cases} \Pr[y_i^* = 1 \mid \underline{\phi}_{(m-1)}, \underline{X}^{(m-1)}, \underline{y_i = 1}] = 1 \\ \Pr[y_i^* = -1 \mid \underline{\phi}_{(m-1)}, \underline{X}^{(m-1)}, \underline{y_i = 1}] = 0 \end{cases}$$

$$\pi_i^{(m)} = \Pr[y_i^* = 1 \mid \underline{\phi}_{(m-1)}, \underline{X}^{(m-1)}, \underline{y_i = -1}]$$

$$\ln \frac{\pi_i^{(m)}}{1-\pi_i^{(m)}} = \ln \frac{\pi_i^{(m-1)}}{1-\pi_i^{(m-1)}} + \beta_{m-1}(X_i^{(m-1)} - \overline{X^{(m-1)}})$$

$$= \ln \frac{\boxed{\pi_i^{(0)}}}{1-\pi_i^{(0)}} + \sum_{j=1}^{m-1} \beta_j (X_i^{(j)} - \overline{X^{(j)}})$$

Initial value: P_0